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GLA c.160C>T (p.L54F) Variant in a Family With Fabry Disease: A Confirmatory Clinical Observation With Biopsy-Proven Kidney Involvement

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Fabry disease (FD) is an X-linked lysosomal disorder caused by pathogenic variants in the *GLA* gene, leading to impaired α-galactosidase A (α-GAL) activity.[1] Although more than a thousand GLA variants have been reported, the pathogenic relevance of many remains uncertain and often requires clinical, biochemical, and segregation data for clarification.[1,2] We present a family carrying the GLA c.160C>T (p.L54F) substitution, providing additional evidence of its clinical significance. A 51-year-old woman was evaluated for persistent microscopic hematuria and non-nephrotic proteinuria. Written informed consent was obtained from the patients. She had nonspecific symptoms, including musculoskeletal pain, fatigue, distal paresthesias, and occasional heat intolerance. Neurological and cardiological examinations were unremarkable, and electromyography and echocardiographic evaluations were also normal. Serum creatinine was 1.2 mg/dL, and 24-hour proteinuria measured 1.2 g/day. Autoimmune and viral markers were negative. Kidney biopsy showed vacuolization of podocytes and glomerular endothelial cells, mesangial matrix expansion, and segmental sclerosis. Immunofluorescence was negative. Oil Red staining showed a lipid-positive pattern, consistent with Fabry nephropathy. Biochemical testing demonstrated mildly reduced α-GAL activity (2.06 nmol/h/mg; ref >2.5) and markedly elevated lyso-Gb3 (8.75 ng/mL; ref <1.3). Genetic analysis identified a heterozygous GLA c.160C>T (p.L54F) variant. Following confirmation in the proband, family screening was performed. Her 23-year-old son carried the same variant in hemizygous form and exhibited a profound reduction in α-GAL activity (0.1 nmol/h/mg). Two heterozygous daughters had preserved enzyme activity and normal lyso-Gb3 levels, consistent with expected variability among female carriers. The youngest daughter tested negative and showed normal biochemical parameters. Although this variant has been previously reported, clinical data remain limited.[3] Our observation provides additional evidence supporting its potential pathogenic role. First, the segregation pattern within the family is consistent with X-linked inheritance: the hemizygous male showed marked biochemical deficiency, whereas female carriers showed variable expression. Second, the proband had characteristic kidneypathology and elevated lyso-Gb3, a sensitive biomarker of disease activity, even when α-GAL levels were only moderately reduced in heterozygous women. Third, the combination of clinical, biochemical, and histological evidence strongly aligns with a Fabry phenotype. From the perspective of variant interpretation, the c.160C>T (p.L54F) substitution fulfills several ACMG/AMP criteria suggestive of pathogenicity: segregation with disease-related biomarkers (PP1), a characteristic clinical presentation (PP4), location in a functionally relevant region of the protein (PM1), and absence from population databases (PM2). Although functional assays are not available, these findings provide supportive evidence for the clinical relevance of this variant.[4] In the ClinVar registry, this

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variant is classified as pathogenic for FD.[5] Notably, 2 of the previously reported cases carrying the GLA p.Leu54Phe (c.160C>T) variant originate from Türkiye. Although this observation is insufficient to draw conclusions regarding population prevalence, it may suggest a regional clustering or under-recognition of this variant in the Turkish population. Further population-based genetic and epidemiological studies are needed to clarify whether this represents a founder effect or reflects limited reporting from other regions. In conclusion, this family provides confirmatory observation linking the c.160C>T (p.L54F) GLA variant with Fabry-related biochemical abnormalities and kidney involvement. We believe this case provides additional data on this variant and may aid future genotype–phenotype assessments.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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REFERENCES

1. Saito S, Ohno K, Sakuraba H. Fabry-database.org: database of the clinical phenotypes, genotypes and mutant α-galactosidase A structures in Fabry disease. *Fabry-database.org*. *J Hum Genet*. 2011;56(6):467-468. [CrossRef]
2. Ishii S, Sakuraba H, Suzuki Y. Point mutations in the upstream region of the α-galactosidase A gene exon 6 in an atypical variant of Fabry disease. *Hum Genet*. 1992;89(1):29-32. [CrossRef]
3. Babur Güler G, Güler A, Doğan A, et al. An overlooked family with a rare mutation for Fabry disease. *Turk Kardiyol Dern Ars*. 2025;53(4):281-285. [CrossRef]
4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. [CrossRef]
5. National Center for Biotechnology Information. ClinVar; [VCV004087288.1]. https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV004087288.1